Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration – data from Australia and the Netherlands

John McGrath MBBS, PhD FRANZCP[1]

Jean-Paul Selten MD, PhD[2]

David Chant PhD[1]

[1] Queensland Centre for Schizophrenia Research, Wolston Park Hospital

[2] Department of Psychiatry, University of Utrecht, The Netherlands

Address correspondence to:
Associate Professor John McGrath
Queensland Centre for Schizophrenia Research
Wolston Park Hospital
Wacol, Q4076
Australia
Phone: +61 7 3271 8595
Fax: +61 7 3271 9567
Email: jjm@brain.wph.uq.edu.au

Acknowledgments: The Stanley Foundation supported this project. We are indebted to Elizabeth Cantor-Graae, Assen Jablensky, Robert Kendell, Michael Kimlin, Tom McNeil, Alfio Parisi, Jaana Suvisaari, Joris Slaets, and the staff of the Queensland Centre for Schizophrenia Research for providing constructive feedback on earlier drafts of this paper:

Key words: schizophrenia, epidemiology, sunshine, age of onset

Abstract

Background

Based on the well-described excess of schizophrenia births in winter and spring, we hypothesised that individuals with schizophrenia (a) would be more likely to be born during periods of decreased perinatal sunshine, and (b) those born during periods of less sunshine would have an earlier age of first registration.

Methods

We undertook an ecological analysis of long-term trends in perinatal sunshine duration and schizophrenia birth rates based on two mental health registers (Queensland, Australia n = 6,630; The Netherlands n=24,474). For each of the 480 months between 1931 and 1970, the agreement between slopes of the trends in psychosis and long-term sunshine duration series were assessed. Age at first registration was assessed by quartiles of long-term trends in perinatal sunshine duration. Males and females were assessed separately.

Results

Both the Dutch and Australian data showed a statistically significant association between falling long-term trends in sunshine duration around the time of birth and rising schizophrenia birth rates for males only. In both the Dutch and Australian data there were significant associations between earlier age of first registration and reduced long-term trends in sunshine duration around the time of birth for both males and females.

Conclusions

A measure of long-term trends in perinatal sunshine duration was associated with two epidemiological features of schizophrenia in two separate data sets. Exposures related to sunshine duration warrant further consideration in schizophrenia research.

Background

One of the most robust epidemiological findings in schizophrenia is the relative excess of schizophrenia births in winter and spring (Bradbury and Miller, 1985; Torrey et al., 1997). Season of birth is thought to act as a proxy marker for an exposure that operates during the pre/perinatal period. The nature of this seasonally-fluctuating risk factor, however, remains unknown. Candidate exposures have included perinatal exposure to winter viruses (Yolken and Torrey, 1995) and seasonal fluctuations in maternal nutrition (Brown et al., 1996; Torrey et al., 1997). Low maternal vitamin D (which depends primarily on exposure to bright sunshine)(McGrath, 1999) and hormonal fluctuations as a consequence of changes in light intensity (Quested, 1996) and have also been proposed as candidate exposures that may underlie the seasonality of schizophrenia births.

In order to refine the search for candidate exposures causally related to the seasonality of schizophrenia births, it seems logical to focus on environmental factors that fluctuate across seasons. For example, the association between temperature and schizophrenia births has been investigated by several groups, however the results of this research has been inconsistent (Welham et al, 2000). Sunshine duration (the hours of bright sunshine per day), photoperiod (the hours between sunrise and sunset per day, regardless of cloud cover and rain) and sunshine intensity (watts per square metre (W m^{-2}), also known as irradiance) each have seasonal fluctuations. These and other sunshine-related variables may serve as potential candidate exposures as it is feasible that they may influence viral, hormonal or nutritional factors that then directly or indirectly impact on brain development. In this paper we will examine the links between sunshine duration and aspects of schizophrenia epidemiology.

Apart from the predictable seasonal (within-year) periodicity in sunshine duration, there are also irregular but substantial between-year fluctuations in sunshine duration. These intra-decadal fluctuations are related to larger climate systems (Glantz et al., 1991). To complement the within-year nature of season of birth studies, where many decades of data are often lumped into seasons or quarters for analysis, this study will examine the associations between these long-term (between-year) fluctuations in sunshine duration and schizophrenia birth rates. Long-term trends capture fluctuations that may span many years. Based on the association between winter/spring and increased schizophrenia births, we hypothesised that schizophrenia birth rates would be inversely associated with long-term trends in perinatal sunshine duration. More specifically, we hypothesised that schizophrenia birth rates would rise during times when long-term trends in perinatal sunshine duration were falling, and schizophrenia birth rates would fall during times when long-term trends in perinatal sunshine duration were rising.

Earlier age of onset has been associated with risk factors for schizophrenia such as family history (Suvisaari et al., 1998) and obstetric complications (Verdoux et al., 1997). Several studies have sought to find a relationship between season of birth and age of onset, however the results of these studies have been inconsistent (Torrey et al., 1997). We decided to explore the association between long-term trends in perinatal sunshine duration and age of onset. However, in the absence of reliable data on age of onset, we have had to rely on age at first registration (the age when an individual first receives

a discharge diagnosis of schizophrenia within a mental health register). Based on the links between other risk factors and age of first registration, we hypothesised that lower long-term trends in perinatal sunshine would be associated with an earlier age of first registration.

PARTICIPANTS AND METHODS

Participants

The data were extracted from two mental health registers for the same time periods, and analysed in an identical fashion. The Queensland Mental Health Statistics System is a name-linked mental health register that covers all those treated in public psychiatric facilities throughout the Australian state of Queensland. Anonymous data on psychiatric admissions in the Netherlands were obtained from the Stichting Informatie Gezondheidszorg (SIG; Foundation for Information on Health Care). Date of birth was extracted for those individuals admitted between 1972 and 1994 who were born in their respective countries between 1931 and 1970 and who received a discharge diagnosis of schizophrenia (International Classification of Diseases 8/9 = 295.x) on at least one occasion. A monthly cumulative incidence rate per 10,000 births (also referred to as birth rate) was used as the basis of the analyses.

Exposures

The Australian Bureau of Meteorology and the Koninklijk Nederlands Meteorologisch Instituut (Royal Dutch Meteorological Institute) provided data from which mean daily hours of sunshine, averaged across monthly periods, could be derived. Duration of bright sunshine was measured in hours with a Campbell-Stokes sunshine duration recorder (one located in Brisbane, the capital city of Queensland located in the south-east corner of the state; the other located at De Bilt, in the centre of The Netherlands). The Campbell-Stokes sunshine duration recorder is a glass sphere that focuses the sun's rays to an intense spot, which will char a mark on a curved card mounted concentrically with the sphere. As the earth rotates, the position of the focused light moves across the card, leaving a mark on the calibrated card. When the sun is obscured, the trace is interrupted. At the end of the day the total length of the trace, less gaps, is proportional to the duration of sunshine. Apart from seasonal changes in photoperiod, climate factors (e.g. cloud cover, fog, rain) and pollution can also reduce the hours of bright sunshine. While Campbell Stokes recorders have been widely used over the last century, since the late 1970s electronic radiometers have been able to more accurately measure radiation. The correlation between sunshine duration (based on the Campbell Stokes recorder) and a calibrated electronic ultraviolet (UV) meter (model 501, Solar Light Co., Philadelphia, PA) has recently been examined in Queensland (McGrath et al, 2001). The erythemal UV meter records solar UV between 295 to 385nm, weighting the output of the sensor by that of the erythemal action spectrum (i.e. those wavelengths implicated in sunburn, DNA damage and the production of previtamin D). Based on mean monthly values recorded over 33 months, we found a statistically significant positive correlation between duration of sunshine and the UV measure (Pearson $r = 0.67$, $p < 0.001$).

Statistical methods

In order to consistently assess between-year variation, both the schizophrenia and sunshine time series were first seasonally adjusted using the SAS 8 implementation of the X-11 seasonal adjustment program developed by the U.S. Bureau of the Census and Statistics Canada (SAS, 1998; Dagum, 1988). The program seasonally adjusts monthly time series on the assumption that seasonal fluctuations S_t can be measured in the original series, O_t, $t = 1,...,n$, and separated from trend cycle C_t, and irregular fluctuations I_t, by the decomposition $O_t = S_t + C_t + I_t$. The trend cycle components, which include variation due to long-term trend and long-term cyclical factors, were used in our tests for association. In the analyses and in the figures, hours of sunshine were inverted in order to conform with the hypothesised relationship between decreased long-term trend in perinatal sunshine duration and increased schizophrenia birth rates. For all analyses, an alpha level of 0.05 was adopted. All p values are two-tailed

Slope Agreement

Having determined two covarying trend series $\{C_t, C'_t\}_{t=1}^{n}$, a test of the null hypothesis that the observed pattern of association between them could have occurred by chance was addressed by fitting a cubic spline independently to each series in order to estimate the series of gradients $\{G_t, G'_t\}_{t=1}^{n}$, and thus derive the series of signs of the gradients $\{Z_t, Z'_t\}_{t=1}^{n}$, where Z_t and Z'_t are -1 if G_t is negative, 0 if G_t is zero, and 1 if G_t is positive. The signs permit robust, non-parametric tests of the hypothesis of chance association using Cohen's kappa as the measure of inter-series agreement, and avoids problems with the non-periodic trend, the magnitude, and the amplitude of $\{G_t, G'_t\}_{t=1}^{n}$, all unduly influencing Pearsonian correlational measures (Agresti, 1990; Cohen, 1960; Fleiss, 1981). The essential features of the technique are shown in Figure 1, using the 1950-1954 extract of the data for Queensland males shown in Figure 2. For each month the signs of the two time series are shown ("+" for rising slopes, "-" for falling slopes), and for each month when the two time series are in agreement, an open box is shown along the horizontal axis. The ratio of number of months with slope agreement and the total months assessed is also shown in Figures 4 and 5.

Insert Figure 1 about here

Sunshine and age at first registration

Sunshine duration at birth was divided into four equal categories (quartiles) and kernel density estimators of age at first registration were plotted for each quartile

(Silverman, 1986). All analyses were conducted on males and females separately. Wilcoxon tests were used to test association between sunshine quartiles and age of first registration. Because age at first registration lags behind age of onset (Welham et al., 1996), we undertook two additional analyses. For the Queensland data, we examined the association between perinatal sunshine duration and age of first registration in a subset of cases (n = 2,583) for which additional register-based information confirmed that that their age at first registration was indeed their first-ever admission for schizophrenia. For the Dutch data, we had sufficient sample size to allow the examination of the association between perinatal sunshine duration and age of first registration in an “early-onset” subgroup (those born between 1950 and 1970, n = 15,308). Because the Dutch register opened in 1970, the age of first registration for the 1950-1970 born group would be more reliable than the age of first registration for the 1931-1949 born group.

Results

In the Queensland data, we identified 4,165 males and 2,465 females for analysis. In the Dutch data, we identified 14,239 males and 10,235 females. Both visual inspection of the time series for male and female schizophrenia birth rates in both countries (see Figure 2), and spectral analysis (data not shown)(Priestley, 1982), suggests substantial between-year variability. In both The Netherlands and Queensland, there was also substantial between-year variability in seasonally adjusted sunshine duration (see Figure 3). Figure 3 also illustrates how seasonal adjustment and the fitting of long-term trend lines “smooth” the within-year fluctuations in order to emphasise the between-year variability. The overall shape of the curves is the result of the interaction of the age of onset of schizophrenia, the included dates of births and the period of operation of the mental health registers.

Insert Figures 2 and 3 about here

Figures 4 and 5 show the association between the trend in schizophrenia birth rates and the long-term trend in perinatal sunshine duration, by sex and country. The months when the two time series are in agreement (either both rising or both falling) are shown along the horizontal axis in each figure as is the ratio of months with slope agreement/total months assessed.

Insert Figures 4 and 5 about here

There were statistically significant agreements between the trend cycles in the male schizophrenia birth rates and long-term trend in perinatal sunshine duration for both the Queensland and Dutch data sets (kappa = 0.186, p = .002; kappa = 0.113, p = .004 respectively). We did not detect any significant agreement between falling long-term trend in perinatal sunshine duration and increasing risk of schizophrenia in females based on either the Queensland or Dutch data (kappa = 0.018, p = .54; kappa = -0.106, p = .004 respectively). The negative kappa for the Dutch women found significant agreement between rising long-term trend in perinatal sunshine duration and rising schizophrenia birth rate – a finding opposite to that predicted.

As expected, both mental health registers revealed sex differences in the peak age of first admission, with men having an earlier median age of first admissions compared to women. For both data sets, there were significant associations between lower long-term trend in perinatal sunshine duration and earlier ages of first registration for both males and females (see Table). In the Queensland data, significant associations were found in both the more reliable "first-ever admission" subsample and in the entire sample. Likewise, in the Dutch data, there were significant associations between lower long-term trend in perinatal sunshine quartiles and earlier age of first registration in both the sample born between 1950-1970 and in the entire sample.

Table 1 about here

Note that the relationship does not appear to be strictly monotonic in the Queensland data, with the quartile with the greatest duration of long-term trend in perinatal sunshine duration associated with a slightly earlier age of first admission than the third quartile for both males and females. Figure 6 shows the density estimators of age of first admission associated with quartiles of the sunshine trend variable for Queensland and the Netherlands. Figure 6 also emphasizes the greater heterogeneity in age of onset for females

Figure 6 about here

COMMENT

Main findings

This paper reports, for the first time, associations between long-term trend in perinatal sunshine duration, schizophrenia birth rates, and age at first registration for schizophrenia. The data, drawn from two mental health registers, are in broad agreement – there was an association between falling long-term trend in perinatal sunshine duration and rising schizophrenia birth rates for males but not for females. Individuals with schizophrenia born in periods with less bright sunshine (as assessed on long-term trends) had earlier ages of first registration. These results suggest that long-term trends in sunshine duration warrants further investigation in schizophrenia risk-factor epidemiology.

The slope agreement method designed for this study can be used to examine the association between birth rates for schizophrenia (or other disorders) and a wide range of candidate exposures. The method complements previous studies which have assessed over-dispersion in schizophrenia birth rates (Kendell and Adams, 1991; Torrey and Rawlings, 1996) by providing a robust, nonparametric method to assess the association between candidate exposures and schizophrenia birth rates.

Limitations

The two mental health registers used in this study were designed primarily for administrative purposes, thus the reliability of diagnosis may be suboptimal. The Dutch data may underestimate the true schizophrenia birth rates due to under-diagnosis by clinicians (Selten and Slaets, 1994). On the other hand, the Queensland register may overestimate the true schizophrenia birth rates as those cases born in other Australian states, but admitted to Queensland hospitals, are included in the numerator and only Queensland births are used in the denominator. However, it is unlikely that diagnostic inaccuracies or between-state migration could be systematically linked to fluctuations in perinatal duration of sunshine. Nevertheless, if there was a true association between sunshine duration and schizophrenia birth rates, these limitations would have made the effect more difficult to detect.

We recommend caution in the interpretation of the age of first registration variable. There is a variable lag between true “onset” of psychosis and first registration (Hafner et al., 1994; Welham et al., 1996). For many individuals born in the 1930s and 1940s, we assume that their “true” age of onset/age of first registration predates the introduction of the two mental health registers (both in the early 1970s). Thus, the date of first registration, and therefore the age at first registration, would over-estimate true age of onset for an uncertain proportion of the cases. Restricting the analysis to those born between 1950 to 1970 reduces, but does not eliminate, this issue. However, the association between perinatal sunshine duration and age at first registration was also found for the Queensland “first-ever” admission subsample.

The sunshine variable for Queensland was based on South-east Queensland. During the period of observation, approximately 70-80% of the population lived in this region (Australian Bureau of Statistics, 1999). The remainder of the population of Queensland lived closer to the equator, those potentially being exposed to more sunshine (longer hours of sunshine and more intense radiation). It is feasible that the sunshine slopes for north Queensland, which would have been more tropical, would have differed systematically in direction (i.e rising versus falling) from those used in this study. If the hypothesis linking lower sunshine duration and higher schizophrenia birth rates is correct, we speculate that this feature would have introduced an averaging, or smoothing, process into the schizophrenia birth rates series, which would, in turn, serve to reduce the strength of association seen in the current data. This is less of an issue for The Netherlands, an area that can fit into Queensland forty-one times over.

At this stage, we do not know if these findings are specific for schizophrenia, or may be related to other psychotic and non-psychotic conditions.

While we were able to reject the hypothesis that falling long-term trend in perinatal sunshine duration was associated with increasing schizophrenia birth rates in Dutch females, we found a significant association between the sunshine variable and schizophrenia in the opposite direction (the negative kappa indicates significant agreement between falling long-term trend in perinatal sunshine duration and falling female schizophrenia birth rates). This finding, which defies ready explanation, suggests that the relationship between the sunshine variable and risk of schizophrenia is influenced by gender. The association between long-term trend in perinatal sunshine duration and risk of schizophrenia in males and females needs to be examined with data from more sites in order to clarify this feature. In the meantime, the paradoxical finding linking rising long-term trend in perinatal sunshine duration and rising schizophrenia birth rates in females weakens the internal coherence of the overall analyses and erodes the hypothesis that between-year fluctuations in sunshine duration are somehow linked causally with schizophrenia (Susser, 1991).

Finally, biometeorological variables are strongly intercorrelated (McMichael et al., 1996; Welham et al., 2000b). The measure of duration of bright sunshine used in this study would be associated with climate variables such as cloudiness, precipitation, temperature and humidity. Apart from these factors, a range of individual behaviour patterns would be associated with sunshine duration (outdoor activity versus indoor living, use of leisure time, amount of clothing worn, use of indoor heating etc)(McMichael et al., 1996; Welham et al., 2000b). The complex web of factors that may be associated with sunshine duration is further compounded by the ecological nature of this study. If we assume that duration of sunshine is related to a risk-modifying factor or a risk indicator for schizophrenia, we have no information on the exposure status of the cases.

There is much about the associations between perinatal sunshine duration and schizophrenia that remains unexplained. If low perinatal sunshine duration is somehow causally related to an earlier age of first registration, then one would expect that the site with more sunshine (i.e. Queensland) would have later ages of first registration – this was not found in this study. In addition, if perinatal sunshine duration were somehow causally related to the risk of developing schizophrenia, then we would expect a negative correlation between incidence and latitude. There is little robust data to support this association (Torrey, 1980). There is, however, evidence of an association between higher latitudes and persisting course of illness (Gupta, 1992), which may also explain the association between higher latitudes and higher prevalence of schizophrenia (Welham et al., 2000a). These findings invite speculation that low perinatal sunshine duration may be associated with a more chronic, persisting course of illness.

Our current study extends previous within-year, season of birth studies by concentrating on fluctuations in schizophrenia births over longer time periods. Data from the Queensland and Dutch mental health registers have previously shown variations in schizophrenia births within the year (McGrath et al., 1995; Selten et al., 2000). In Queensland we found schizophrenia births peaked in the third quarter of the year (July, August, September – Southern Hemisphere winter/spring), while the Dutch study identified peak schizophrenia births in May and June (spring/summer) with a pronounced drop in July, August and September (summer/autumn). Future studies will examine these data in more detail in order to explore if the within-year fluctuations are consistently seasonal (i.e have genuine 12-month periodicities), or are evolving in time. In addition, we will explore links between the within-year fluctuations and long-term fluctuations in schizophrenia births rates (e.g. is there more or less within-year fluctuation during periods with rising schizophrenia birth rates; how are the within-year and between-year changes related?).

Interpretation

It is plausible that certain infectious agents are more prevalent during periods of reduced or increased sunshine duration, especially in view of the correlations between biometeorological factors mentioned above. The transmission of infectious agents would be facilitated during periods of indoor confinement, which may be related to rainfall. Overcrowding has been proposed as a risk factor for schizophrenia (Torrey and Yolken, 1998) and rainfall, humidity and sunshine duration may interact with the opportunity for the transmission of infectious agents in overcrowded settings. There is a growing body of literature showing that ultraviolet radiation exposure suppresses both systemic and local immune responses to a variety of antigens, including some microorganisms (Garssen et al., 1998). Ultraviolet radiation can affect viral mutation, viral oncogenesis, activation of viral genomes and the suppression of immune responses to viruses (Norval et al., 1994). It is not clear how the results of this study can be explained by these factors. Perhaps the lack of bright sunshine results in an altered profile of infectious agents and/or an altered host-response to infection such that the development of the fetus and neonate is compromised in some manner.

Some of the links between sunshine and schizophrenia may be mediated by perinatal vitamin D levels (McGrath, 1999). Vitamin D is a steroid hormone derived predominantly from the action of ultraviolet B radiation on the skin. Vitamin D receptors have been found in differentiating zones of the central nervous system of the rat embryo (Veenstra et al., 1998) and in the adult human brain (Stumpf et al., 1982). Vitamin D induces a range of genes involved in brain development including Nerve Growth Factor (Darwish and DeLuca, 1993; Musiol and Feldman, 1997). Because vitamin D production is associated with the duration of the bright sunshine (Webb et al., 1988), variables related to sunshine have been included in epidemiological studies of several diseases with putative links to low vitamin D. Significant associations have been reported for low sunshine and increased risk of disorders such as osteoporosis (Holick, 1995), multiple sclerosis (Norman, Jr. et al., 1983), breast cancer (Garland et al., 1990; Gorham et al., 1990), prostate cancer (Emerson and Weiss, 1992; Hanchette and Schwartz, 1992), colorectal cancer (Emerson and Weiss, 1992; Garland and Garland, 1980; Lipkin and Newmark, 1999), and insulin dependent diabetes mellitus (Nystrom et al., 1992).

Recently we tested the association between duration of sunshine and vitamin D levels in 414 adults living in south-east Queensland (McGrath et al, 2001). As expected, the 25 hydroxyvitamin D_3 levels were significantly positively correlated with mean duration of sunshine during the month of testing. However, the association between these variables may be more complex at high latitudes compared to low latitudes. At latitudes greater than 40 degrees, the ultraviolet radiation during winter is insufficient to produce vitamin D (Webb et al, 1988). The duration of this vitamin D "blackout window" increases with higher latitudes. Holland extends from latitude 51 to 53.5 degrees north, thus the blackout window would extend from approximately October to March. The level of vitamin D at the end of the blackout window would be a function of the half-life of vitamin D and the peak vitamin D level achieved in the previous summer and autumn. The functional half-life of vitamin D is between 2 to 4 weeks, a feature related to the capacity of vitamin D binding protein (Safadi et al, 1999). Therefore, factors that influence the availability of sunshine immediately prior to and after the usual seasonal vitamin D blackout window will also lengthen the period during which the individual must rely on summer-autumn stores of Vitamin D. For example, at the latitude of the Netherlands, reduced sunshine duration (and therefore ultraviolet irradiation levels) during April to September would reduce summer vitamin D stores and result in more hypovitaminosis D by the end of the blackout window in March the following year (a variable lag of between 6 to 11 months). In contrast, reduced sunshine duration after the end of the blackout window in April will increase the incidence of hypovitaminosis D during this same period (zero lag). The use of long-term trends in sunshine reduces, but does not eliminate, the impact of this effect. We are currently developing statistical models that can more precisely capture this issue.

The association between long-term trends in perinatal sunshine duration and schizophrenia birth rates was found for males but not females. The sex-specific nature of this association was not predicted. Based on the results of this study, we suggest that the sunshine-related exposure may be more relevant to early onset male schizophrenia. Castle and Murray (Castle and Murray, 1991) have previously suggested that nongenetic factors may play a dominant role in men with early-onset schizophrenia. While the sunshine variable was not associated with female schizophrenia birth rates, we did find a relationship between this variable and age of first registration in females. The findings raise questions about how the putative exposure interacts with other factors to influence the expression and course of the disorder.

We acknowledge the ecological nature of the analyses, and the inconsistencies in the results of this study. In light of these issues, we are reluctant to speculate further on the meanings of these findings. However, we believe that long-term trends in duration of perinatal sunshine warrant further consideration in schizophrenia research. While risk-factor epidemiology lacks the ability to systematically "map" the environment, ecological studies can provide "hot spots" from which to generate candidate exposures. If the findings linking long-term trends in perinatal sunshine duration and schizophrenia birth rates and age at first registration survive the test of future replications, then we hope that factors related to sunshine duration can help generate novel candidate exposures to help "fine map" nongenetic risk factors for schizophrenia.

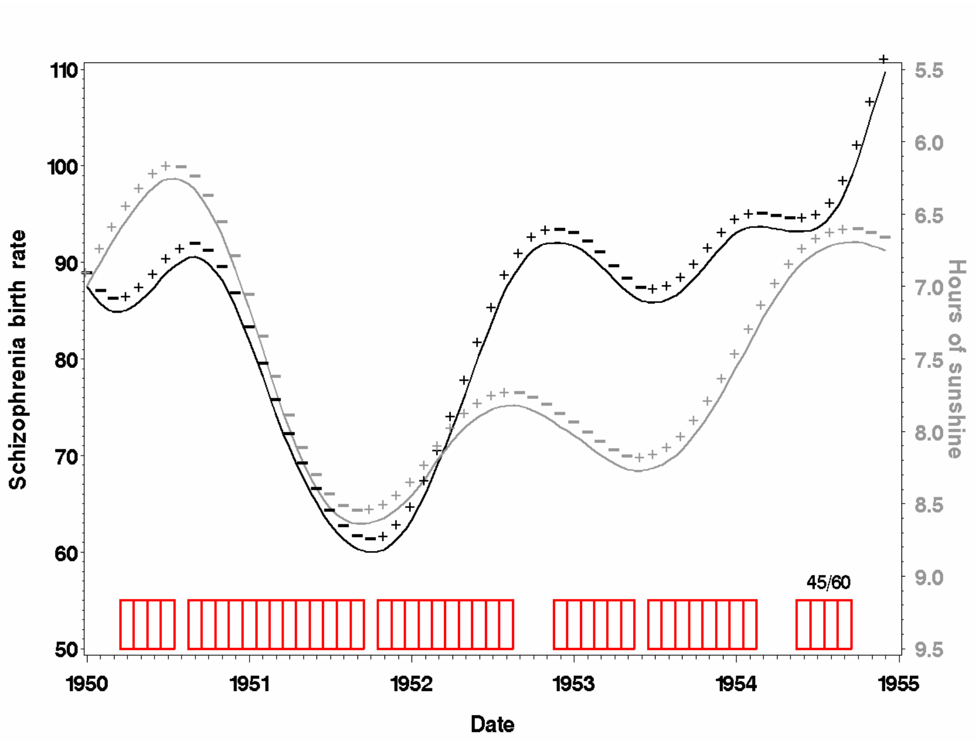


Figure 1. Calculation of slope agreement between male schizophrenia birth rates and duration of sunshine based on Queensland data 1950-1954. Rising slopes are marked with + and falling slopes with -. For each month the signs of the two slopes (either + or -) are assessed for agreement. Months during which the slopes are in agreement are marked with the open box. In this example, the two time series' slopes are in agreement for 45 of the 60 months.

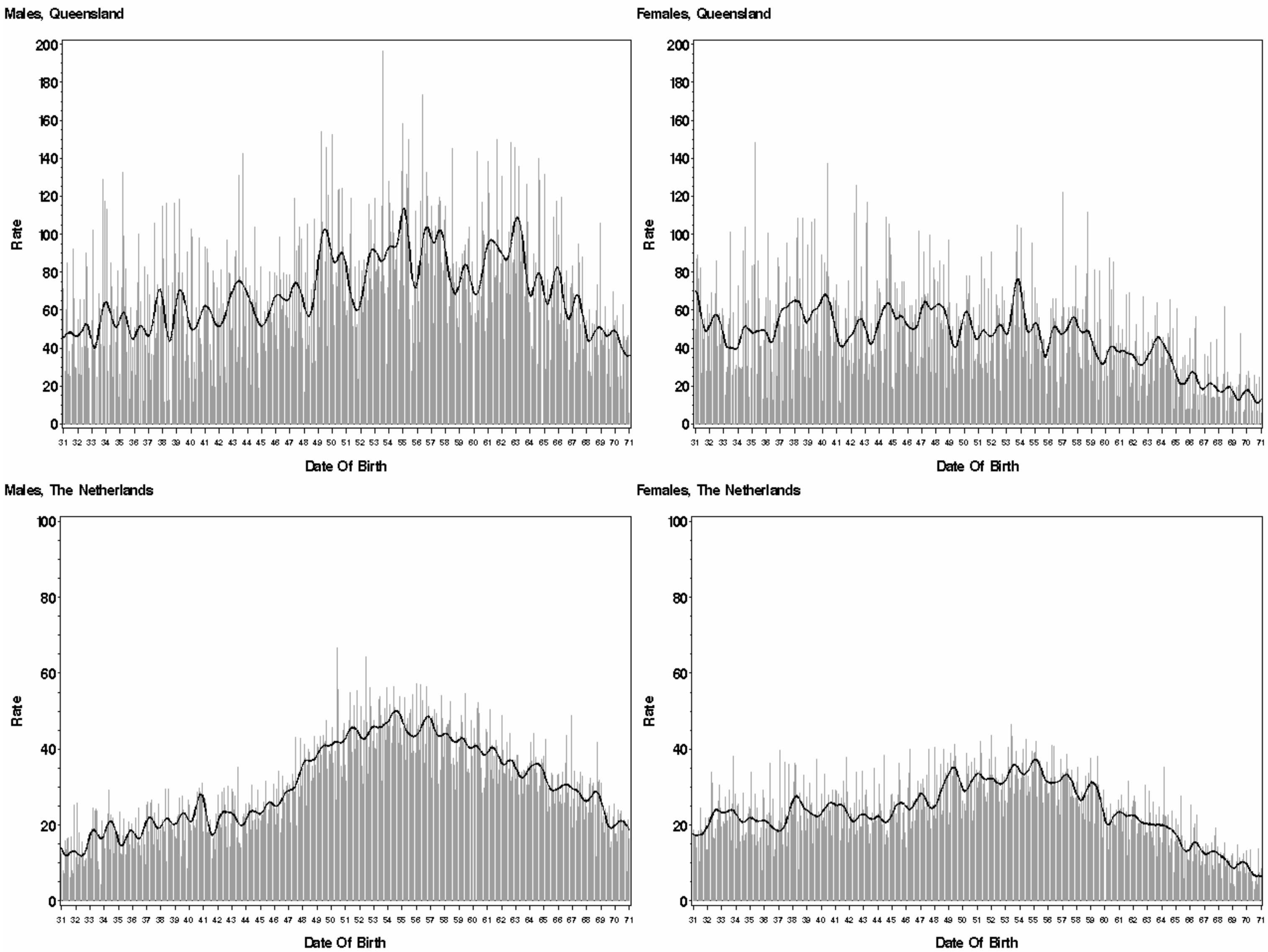
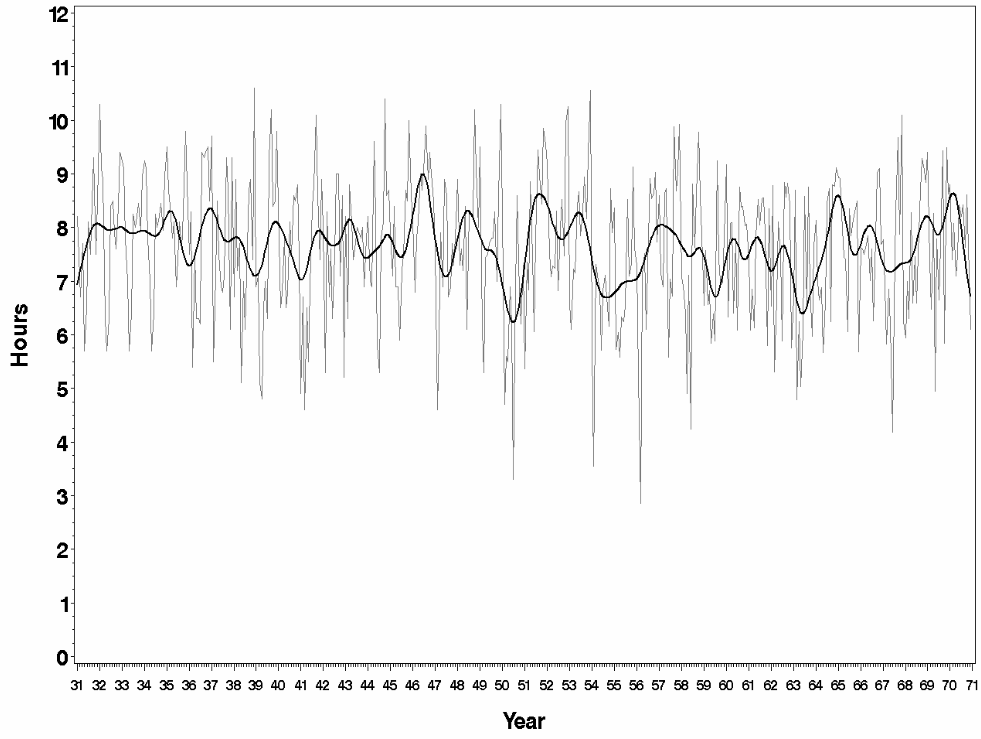


Figure 2. Schizophrenia rates per 10,000 births, by sex, in Queensland and The Netherlands

Queensland



The Netherlands

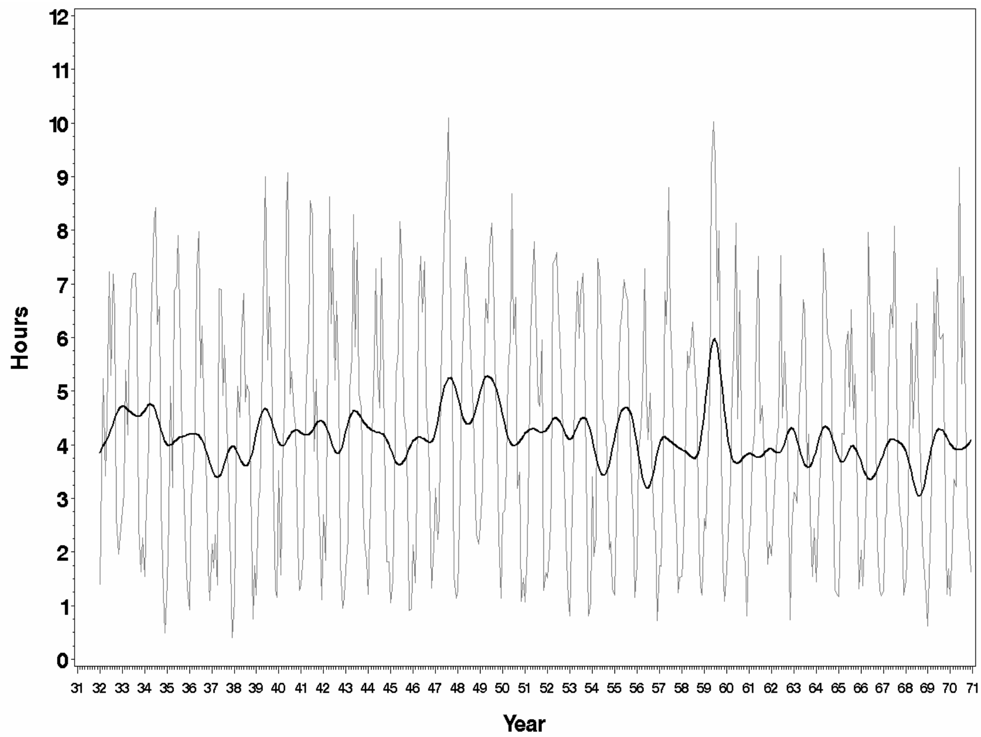
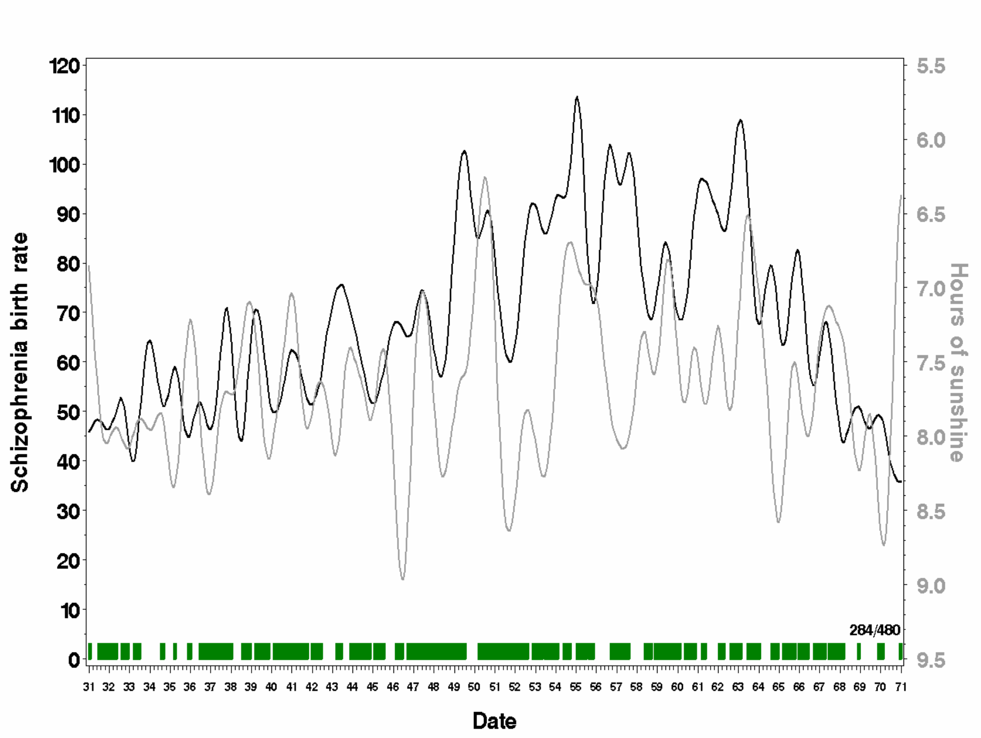


Figure 3 Month on Month Averaged Daily Hours of Sunshine, in Queensland and The Netherlands, with Long Term Trend Superimposed

Queensland



The Netherlands

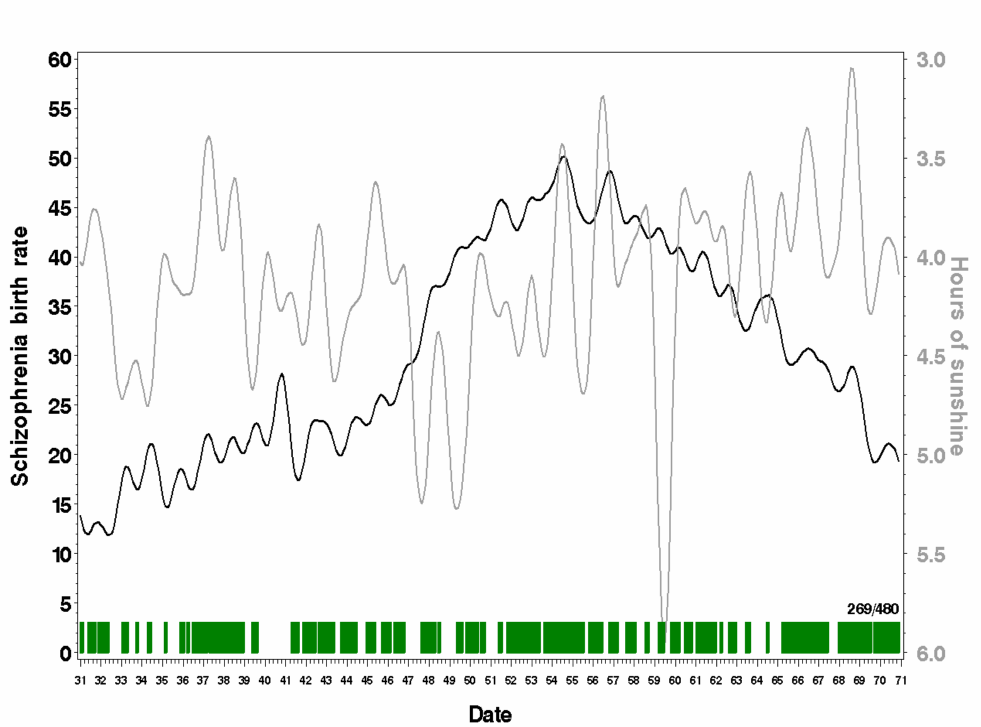
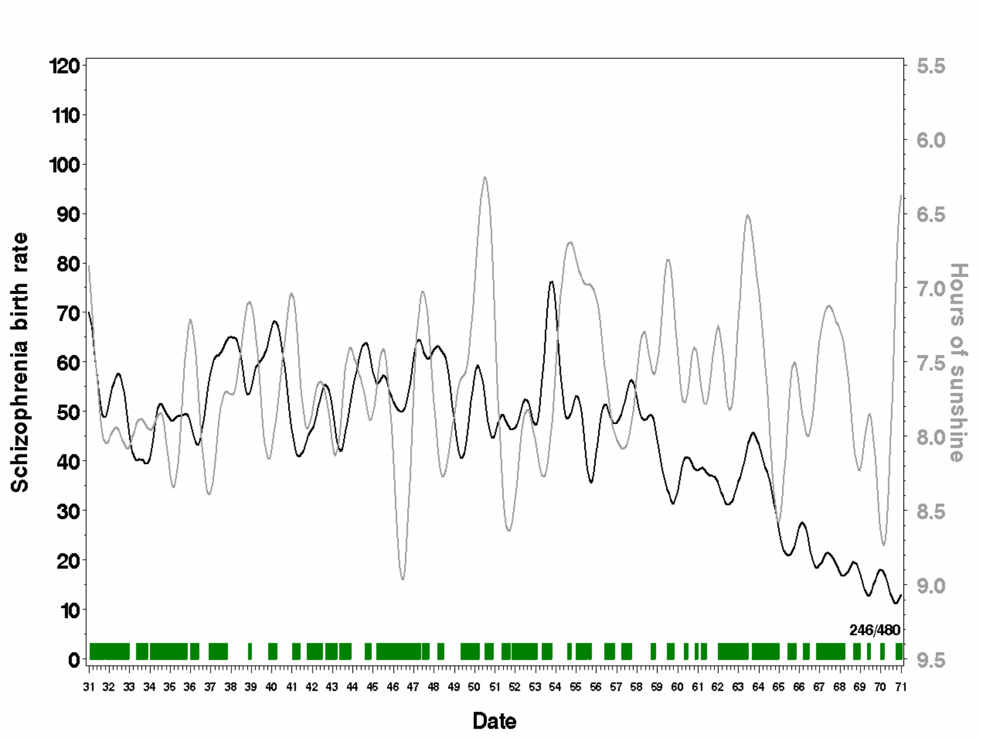


Figure 4. Association Between Trends in Male Schizophrenia and Seasonally Adjusted Hours of Sunshine: Queensland and The Netherlands. The dark band above the horizontal axis mark periods of slope agreement.

Queensland



The Netherlands

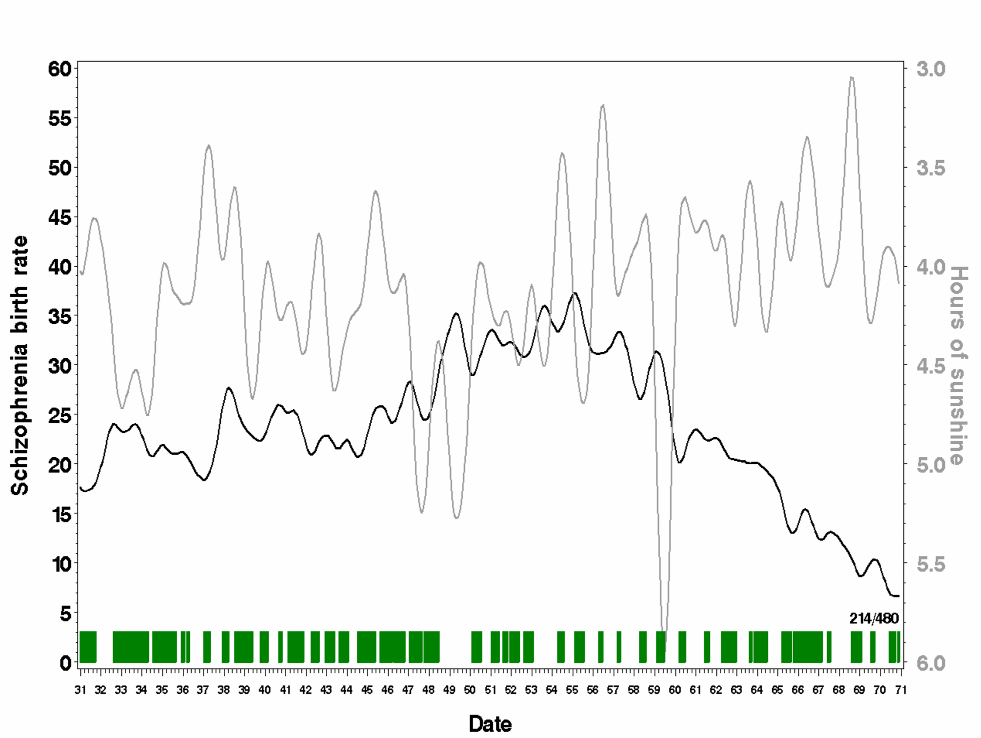


Figure 5. Association Between Trends in Female Schizophrenia and Seasonally Adjusted Hours of Sunshine: Queensland and The Netherlands The dark band above the horizontal axis mark periods of slope agreement.

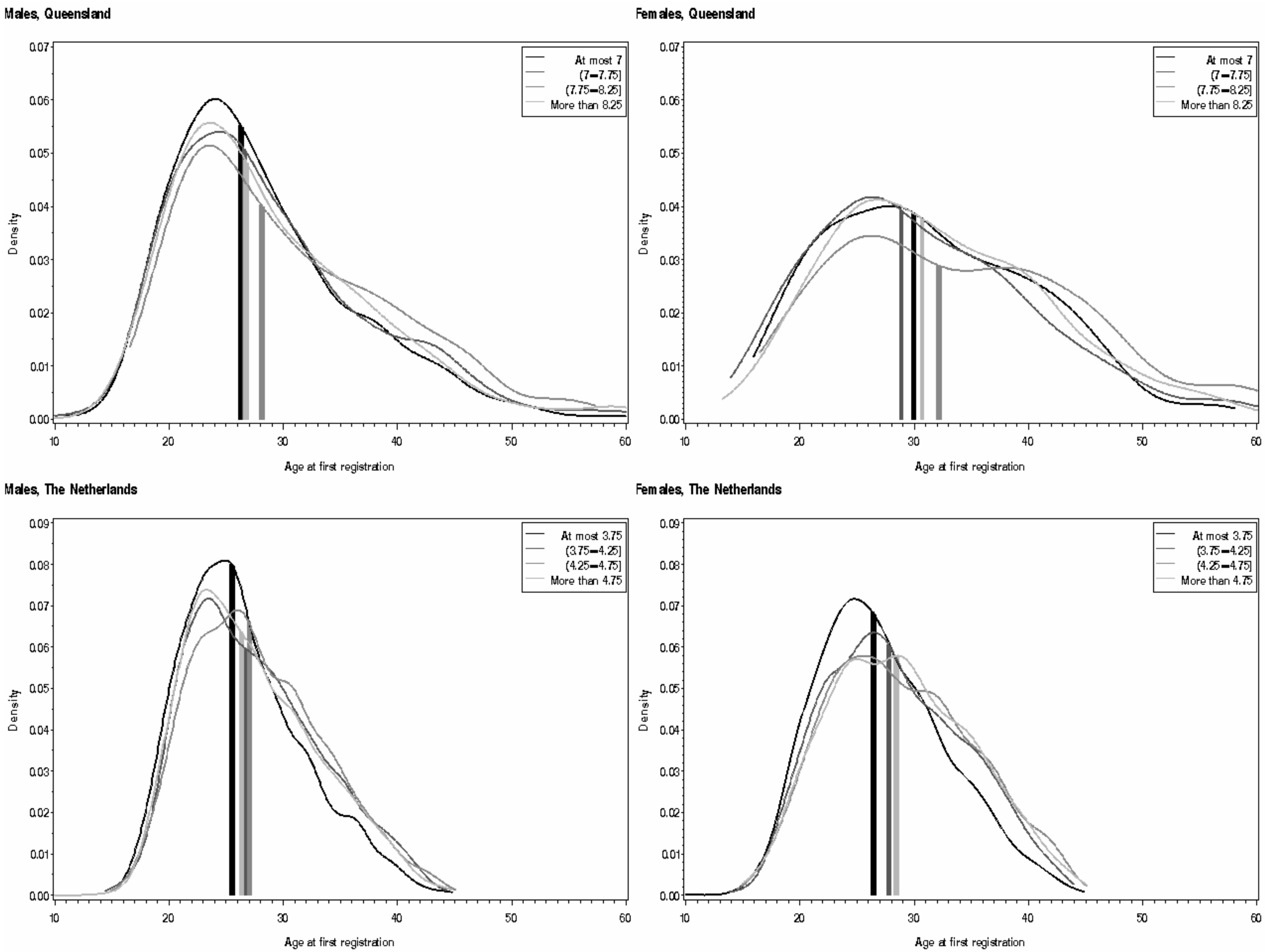


Figure 6. Densities of age of first registration, for quartiles of long-term trend in perinatal sunshine duration, by sex and country

Table 1. Median age at first registration, and sample size, by sex and country

		Quartile of Sunshine Duration				
		1	2	3	4	Overall
Netherlands	Males	28.0	29.6	30.2	30.3	29.3
- entire	(*p* < .001)	(4,263)	(3,702)	(2,917)	(3,357)	(14,239)
sample	Females	31.3	33.0	33.9	34.5	33.0
	(*p* <.001)	(2,871)	(2,727)	(2,130)	(2,507)	(10,235)
Netherlands	Males	25.5	26.7	27.0	26.4	26.3
- 1950-1970	(*p* < .001)	(3,138)	(2,641)	(2,107)	(1,843)	(9,639)
born sample	Females	26.4	27.8	28.4	28.5	27.5
	(*p* < .001)	(1,737)	(1,619)	(1,192)	(1,121)	(5,669)
Queensland	Males	27.9	27.9	30.0	29.0	28.5
- entire	(*p* <.001)	(1,140)	(1,162)	(792)	(1,071)	(4,165)
sample	Females	31.4	32.0	35.0	32.8	32.5
	(*p* <.001)	(597)	(623)	(521)	(724)	(2,465)
Queensland	Males	26.3	26.6	28.2	26.7	26.8
- "first-ever	(*p* = .02)	(464)	(495)	(336)	(421)	(1,716)
admission"	Females	30.0	28.9	32.2	30.7	30.7
sample	(*p* = .02)	(206)	(210)	(190)	(261)	(867)

Notes: (i) Mean daily sunshine averaged over monthly periods, (a) Queensland: at most 7 hrs., (7-7.5] hrs., (7.5-8.25] hrs., greater than 8.25 hrs.; (b) The Netherlands: at most 3.75 hrs., (3.75-4.25] hrs., (4.25-4.75] hrs., greater than 4.75 hrs.; (ii) sample sizes in parentheses; (iii) *p*-values for the Wilcoxon test between quartiles of sunshine duration.

References

Agresti, A. 1990, Categorical Data Analysis John Wiley & Sons, Inc, New York.

Australian Bureau of Statistics 1999, Australian demography Catalogue 3101.0 Commonwealth Government of Australia, Canberra.

Bradbury, T. N., Miller, G. A., 1985. Season of birth in schizophrenia: A review of evidence, methodology, and etiology. Psychol Bull 98, 569-594.

Brown, A. S., Susser, E. S., Butler, P. D., Richardson, A. R., Kaufmann, C. A., Gorman, J. M., 1996. Neurobiological plausibility of prenatal nutritional deprivation as a risk factor for schizophrenia. J.Nerv.Ment.Dis. 184, 71-85.

Castle, D. J., Murray, R. M., 1991. The neurodevelopmental basis of sex differences in schizophrenia. Psychol Med 21, 565-575.

Cohen, J., 1960. A coefficient of agreement for nominal scales. Ed Psychol Measurement 20, 37-46.

Dagum, E.B. 1988, The X-11 ARIMA/88 Seasonal Adjustment Method, Statistics Canada.

Darwish, H., DeLuca, H. F., 1993. Vitamin D-regulated gene expression. Crit Rev.Eukaryot.Gene Expr. 3, 89-116.

Emerson, J. C., Weiss, N. S., 1992. Colorectal cancer and solar radiation. Cancer Causes Control 3, 95-99.

Fleiss, J. L. 1981, Statistical methods for rates and proportions, 2nd edition, John Wiley & Sons, Inc., New York.

Garland, C. F., Garland, F. C., 1980. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int. J. Epidemiol. 9, 227-231.

Garland, F. C., Garland, C. F., Gorham, E. D., Young, J. F., 1990. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev. Med. 19, 614-622.

Garssen, J., Norval, M., el Ghorr, A., Gibbs, N. K., Jones, C. D., Cerimele, D., De Simone, C., Caffieri, S., Dall'Acqua, F., De Gruijl, F. R., Sontag, Y., Van Loveren, H., 1998. Estimation of the effect of increasing UVB exposure on the human immune system and related resistance to infectious diseases and tumours. J.Photochem.Photobiol.B 42, 167-179.

Glantz, M. H., Katz, R. W., & Nichols, N. 1991, Teleconnections linking worldwide climate anomalies. Cambridge University Press, Cambridge.

Gorham, E. D., Garland, F. C., Garland, C. F., 1990. Sunlight and breast cancer incidence in the USSR. Int.J.Epidemiol. 19, 820-824.

Gupta, S., 1992. Cross-national differences in the frequency and outcome of schizophrenia: a comparison of five hypotheses. Soc.Psychiatry Psychiatr.Epidemiol. 27, 249-252.

Hafner, H., Maurer, K., Loffler, W., Fatkenheuer, B., an der, H. W., Riecher-Rossler, A., Behrens, S., Gattaz, W. F., 1994. The epidemiology of early schizophrenia. Influence of age and gender on onset and early course. Br.J.Psychiatry Suppl,29-38.

Hanchette, C. L., Schwartz, G. G., 1992. Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. Cancer 70, 2861-2869.

Holick, M. F., 1995. Environmental factors that influence the cutaneous production of vitamin D. Am.J.Clin.Nutr. 61, 638S-645S.

Kendell, R. E., Adams, W., 1991. Unexplained fluctuations in the risk for schizophrenia by month and year of birth. Br.J.Psychiatry 158, 758-763.

Lipkin, M., Newmark, H. L., 1999. Vitamin D, calcium and prevention of breast cancer: a review. J.Am.Coll.Nutr. 18, 392S-397S.

McGrath, J., 1999. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophr.Res. 40, 173-177.

McGrath, J., Welham, J., Pemberton, M., 1995. Month of birth, hemisphere of birth and schizophrenia. Br.J Psychiatry 167, 783-785.

McGrath JJ, Kimlin M, Saha S, Eyles D, Parisi A. (2001) Vitamin D insufficiency in south-east Queensland. Medical Journal of Australia. 174; 150-151.

McMichael, A. J., Haines, A., Slooff, R., & Kovats, S. 1996, Climate change and human health. World Health Organization, Geneva.

Musiol, I. M., Feldman, D., 1997. 1,25-Dihydroxyvitamin D-3 induction of nerve growth factor in L929 mouse fibroblasts: Effect of vitamin D receptor regulation and potency of vitamin D-3 analogs. Endocrinology 138, 12-18.

Norman, J. E., Jr., Kurtzke, J. F., Beebe, G. W., 1983. Epidemiology of multiple sclerosis in U.S. veterans: 2. Latitude, climate and the risk of multiple sclerosis. J.Chronic.Dis. 36, 551-559.

Norval, M., el Ghorr, A., Garssen, J., Van Loveren, H., 1994. The effects of ultraviolet light irradiation on viral infections. Br.J.Dermatol. 130, 693-700.

Nystrom, L., Dahlquist, G., Ostman, J., Wall, S., Arnqvist, H., Blohme, G., Lithner, F., Littorin, B., Schersten, B., Wibell, L., 1992. Risk of developing insulin-dependent diabetes mellitus (IDDM) before 35 years of age: indications of climatological determinants for age at onset. Int.J.Epidemiol. 21, 352-358.

Priestley, M. B. 1982, Spectral analysis and time series Academic Press, Inc., New York.

Quested, D. J., 1996. If Schizophrenia is enantiomorphism, is light the morphogen? Med.Hypotheses 46, 233-238.

Safadi FF, Thornton P, Magiera H, Hollis BW, Gentile M, Haddad JG, Liebhaber SA, Cooke NE (1999) Osteopathy and resistance to vitamin D toxicity in mice null for vitamin D binding protein. J Clin Invest;103:239-51.

SAS 1998, SAS/ETS online user's guide, Version 7 SAS Institute Inc., Cary, NC.

Selten, J. P., Slaets, J. P., 1994. Evidence against maternal influenza as a risk factor for schizophrenia. Br.J.Psychiatry 164, 674-676.

Selten, J. P., van der, G. Y., Dijkgraaf, M., Edlinger, M., Kahn, R., 2000. Seasonality of schizophrenia and stillbirths in The Netherlands. Schizophrenia Research 44, 105-111.

Silverman, B. W. 1986, Density estimation for statistics and data analysis. Chapman and Hall, London.

Stumpf, W. E., Sar, M., Clark, S. A., DeLuca, H. F., 1982. Brain target sites for 1,25-dihydroxyvitamin D3. Science 215, 1402-1405.

Susser, M., 1991. What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epidemiology 133, 635-648.

Suvisaari, J. M., Haukka, J., Tanskanen, A., Lonnqvist, J. K., 1998. Age at onset and outcome in schizophrenia are related to the degree of familial loading. Br.J Psychiatry 173, 494-500.

Torrey, E. F. 1980, Schizophrenia and civilization. Jason Aronson, New York.

Torrey, E. F., Miller, J., Rawlings, R., Yolken, R. H., 1997. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. Schizophrenia Research 28, 1-38.

Torrey, E. F., Rawlings, R. R., 1996. Fluctuations in schizophrenic births by year. Br.J.Psychiatry 169, 772-775.

Torrey, E. F., Yolken, R. H., 1998. At issue: is household crowding a risk factor for schizophrenia and bipolar disorder? Schizophr.Bull. 24, 321-324.

Veenstra, T. D., Prüfer, K., Koenigsberger, C., Brimijoin, S. W., Grande, J. P., Kumar, R., 1998. 1,25-Dihydroxyvitamin D_3 receptors in the central nervous system of the rat embryo. Brain Research 804, 193-205.

Verdoux, H., Geddes, J. R., Takei, N., Lawrie, S. M., Bovet, P., Eagles, J. M., Heun, R., McCreadie, R. G., McNeil, T. F., O'Callaghan, E., Stober, G., Willinger, M. U., Wright, P., Murray, R. M., 1997. Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. Am J Psychiatry 154, 1220-1227.

Webb, A. R., Kline, L., Holick, M. F., 1988. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J.Clin.Endocrinol.Metab. 67, 373-378.

Welham, J., Davies, G., Auliciems, A., & McGrath, J 2000. Climate, geography and the search for candidate nongenetic risk factors for schizophrenia. Int J Mental Health 29, 79-100.

Welham, J. L., Pemberton, M. R., McGrath, J. J., 1996. Incorporating lag effects in register-based age-of-onset distributions in schizophrenia. Schizophr.Res. 20, 125-132.

Yolken, R. H., Torrey, E. F., 1995. Viruses, schizophrenia and bipolar disorder. Clin.Micro.Rev. 8, 131-145.